## **EXHIBIT 1**

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Paper: Request for Reconsideration, Transmittal Form, Fee Transmittal (In duplicate), return

card all sent via U.S. First Class Mall Applicant(s): Stephen Donovan

Title: Transdermal Botulinum Toxin Administration
Serial No: 09/675,172 Filing Date: September 29, 2003
Docket No. ALLE0016-102 (17510 DIV2) [165596]

Date Sent: Oct 31/05

By: Quan L. Nguyen/cda

NOV 8 2005



PTO/SB/21 (09-04)

Approve se through 07/31/2008. OMB 0851-0031

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TRANSMITTA	Application Number 09/675,172			72		
FORM		Filing Date		September 29, 2003		
		First Named Inventor		Stephen Donovan		
1		Art Unit		1645		
(to be used for all correspondence efter initial filing)		Examiner Name		Vanessa L. Ford		
Total Number of Pages In This Submis	slon	Attorney Docket N	umber	ALLE0016	5-102 (17510 DIV2)	[165596]
	ENCLO	SURES (check all tha	t apply)			
Fee Transmittal Form	☐ Drawing(s) ☐ After Allowance Commun				llowance Communic	ation to TC
Fee Attached	Licensing-	related Papers		Appeal Communication to Board of Appeals and Interferences		
Amendment / Reply	Petition			Appeal Communication to TC (Appeal Notice, Briof, Repty Briof)		
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Affidavits/declaration(s)	Power of Attorney, Revocation Change of Correspondence Address			Status Letter		
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Signature	(h		_			
Typed or printed name Quan L. N	guyen			Date	10/3/05	

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a banefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to 12 minutes to complete, including pathoring, preparing, and submitting the completed application form to the USPTO. The will very depending upon the individual case. Any comments on the amount of time you require to complete this form antior suggestions for routeding this burden, should be sent to the Chief information Officer, U.S. Patent and Tradomark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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1-020 P.000/013 P-408

proved for use through 07/31/2006, OMB 0651-0032 ademark Office; U.S. DEPARTMENT OF COMMERCE U.S. Patent and Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number. Effective on 12/08/2004. Complete if Known Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818). 09/675,172 Application Number FEE TRANSMITTAL September 29, 2003 Filing Date for FY 2005 Stephen Donovan First Named Inventor ☐ Applicant claims small entity status. See 37 CFR 1,27 Examiner Name Vanessa L. Ford Art Unit 1645 **TOTAL AMOUNT OF PAYMENT** 0 (\$) Attorney Docket No. ALLE0016-102 (17510 DIV2) [166596] METHOD OF PAYMENT (check all that apply) ☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify) : Deposit Account Deposit Account Number: 50-1275 Deposit Account Name: Cozen O'Connor For the above-identified deposit account, the Director is hereby authorized to: (check all that apply) Charge fee(s) indicated below Charge fee(s) indicated below, except for the filing fee Charge any additional fee(s) or underpayments of fee(s) Credit any overpayments Under 37 CFR 1.16 and 1.17 WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038. **FEE CALCULATION** 1. BASIC FILING, SEARCH, AND EXAMINATION FEES **SEARCH FEES FILING FEES EXAMINATION FEES Small Entity** Small Entity Small Entity **Application Type** <u>Fee (\$)</u> Fee(\$) Fee(\$) Fee(\$) Fees Paid (\$) Fee(\$) Fee(\$) Utility 300 150 500 250 200 100 Design 200 100 100 50 130 65 Plant 150 200 100 300 160 80 Reissue 300 150 500 250 600 300 **Provisional** 200 100 0 ٥ 2. EXCESS CLAIM FEES Small Entity Fee Description Fee (\$) Fee (\$) Each claim over 20 (including Reissues) 50 25 Each independent claim over 3 (including Reissues) 200 100 360 180 Multiple dependent claims Total Claims Extra Claims Fee Paid (\$) Multiple Dependent Claims Fee(\$) 9 - HP = 35 Ω 0 Fee (\$) Fee Paid (\$) 0 HP = highest number of total claims paid for, if greater than 20. Indep. Claims Extra Claims Fee(\$) Fee Paid (\$) - 3 or HP= 0 0 HP = highest number of independent claims paid for, if greater than 3. If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(c)), the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s). Number of each additional 50 or fraction thereof Fee (\$) Total Sheets Extra Sheets Fee Pald (\$) (round up to a whole number) x - 100 = / 50 = 4. OTHER FEE(S) Fees Paid (\$) Non-English Specification, \$130 fee (no small entity discount) Other (o.g., late filing surcharge): \_

SUBMITTED BY				
Signature	Q-	Registration No. (Attorney/Agent) 48,857	Totaphono	215-665-2168
Name (Print/Type)	Quan Piguyan		Date ie/	21/05

This collection of information is required by 37 CFR 1.136. The information is required to abtain or retain a bonefit by the public which is to fite (and by the USPTO to process) an application. Confidentially is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is califieded to take 30 minutes to complete, including gethering, proporting, and submitting the completed application form to the USPTO. Time will very objection pupon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Population of Office, U.S. Population of Commerce, P.O. Bex 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patenta, P.O. Bex 1450, Alexandria, VA 22313-1450.

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		Filing Date	September 29, 2003				
for FY 2005				First Named Inventor	Stephen Donovs	an	
☐ Applicant claim	s small entity s	tatus. See 37 CFR	1.27	Examiner Name	Vanessa L. Ford		
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Plant	200	100	300	150	160	80	
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SUBMITTED BY		^			<u>.</u>		
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Skinature		<u> </u>		(Attorney/Agent)	46,957	Telephon	0 215-865-2150
Name (Print/Type)	Quan L. Nguyen					Data	17/27/95

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From-COZEN O'CONNOR

DOCKET NO.: ALLE0016-102

(17510 DIV2)

Mar-29-2006 15:13

**PATENT** 

#### IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Examiner:

Stephen Donovan

Vanessa L. Ford

Serial No.:

09/675,172

Group Art Unit:

1645

Filed:

September 29, 2003

Confirmation No.

5916

For:

TRANSDERMAL BOTULINUM TOXIN ADMINISTRATION

Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dear Sir:

#### REQUEST FOR RECONSIDERATION

In response to the Office Action mailed July 29, 2005, in connection with the above-identified patent application, Applicant respectfully requests reconsideration of the rejections of record in view of the remarks provided below.

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#### Listing of Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

- 1-21. (canceled).
- 22. (original) A method of reducing neurotransmitter release in a subdermal structure of a patient, the method comprising the steps of:
- (a) non-chemically disrupting the stratum corneum of the patient's skin to reduce impermeability of the stratum corneum; and
- (b) applying botulinum toxin to the skin of the patient in an area that has had the stratum corneum disrupted in step (a).
- 23. (original) The method of claim 22, wherein the stratum corneum is disrupted by abrasively removing the stratum corneum.
- 24. (original) The method of claim 22, wherein the stratum corneum is disrupted by applying an adhesive material to the patient's skin, and removing the adhesive material applied thereto.
- 25. (original) The method of claim 22, wherein the stratum corneum is disrupted by applying ultrasound at a frequency between 20 kHz and less than 10 MHz at an intensity that does not permanently damage the patient's skin.
- 26. (original) The method of claim 22, wherein the stratum corneum is disrupted by passing electrical current from a first point on the patient's skin to a second point on the patient's skin.

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- 27. (original) The method of claim 26, wherein the electrical current is passed to create a plurality of pores in the stratum corneum to enhance passage of botulinum toxin to the subdermal structures.
- 28. (original) The method of claim 22, wherein the botulinum toxin is selected from a group of botulinum toxins consisting of types A, B, C, D, E, F and G.
- 29. (original) The method of claim 22, wherein the botulinum toxin is applied in a pharmaceutical composition comprising an enhancing agent for enhancing the delivery of the botulinum toxin through the skin.
- 30. (original) The method of claim 22, wherein the botulinum toxin is incorporated into a transfersome.
- 31-35 (canceled).

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#### REMARKS

Upon entry of the above amendment, claims 22-30 will be pending in this application.

#### Yuzhakov et al. Is Not Prior Art

Claims 22 and 26-29 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Pat. No. 6,565,532 to Yuzhakov et al. (hereinafter "the Yuzhakov reference"). Applicant respectfully asserts the claimed invention is novel because the Yuzhakov reference cannot be an anticipating prior art under 35 U.S.C. § 102(e). Specifically, 35 U.S.C. § 102(e) states that an applicant is entitled to a patent, unless:

the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371 (c) of this title [35 USC §371(c)(1), (2), (4)] before the invention thereof by the applicant for patent...

Thus, a reference can only be prior art under 102(e) if it is granted before to the priority date of the claimed invention. The Yuzhakov reference cannot be an anticipating prior art reference under 102(e) because its grant date of May 20, 2003 is after the invention date of the present application, which is as least as early as July 11, 2002 (see Preliminary Amendment filed on September 29, 2003, which amended the specification to state that the present application is a divisional of U.S. Application Serial No. 10/194,805 which was filed July 11, 2002). Accordingly, the claimed invention is novel.

#### The Claims Are Nonobvious

Claims 22-30 stand rejected under 35 U.S.C. § 102(e) as allegedly being obvious over the Yuzhakov reference in view of Mitragotri et al. (Science, Vol. 269, August 11,

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1995, hereinafter "the Mitragotri reference"), U.S. Patent No. 5,587,396 (hereinafter "the Smith reference"), and/or U.S. Patent No. 6,165,500 (hereinafter "the Cevc reference").

The Office Action cites the Yuzhakov reference as the primary reference. However, as stated above, the Yuzhakov reference cannot be cited as prior art. As such, the rejection for obviousness would be based entirely on the cited secondary references. However, none of the secondary references by itself, or in combination with other references, teach or suggest the claimed invention. For example, the claimed invention recites the steps of non-chemically disrupting the stratum corneum and applying a botulinum toxin to the disrupted stratum corneum for the botulinum toxin to penetrate to a subdermal layer of the patient skin. Botulinum toxin is about 150 kDa by itself, and is about 900 kDa when it is associated with other non-toxin proteins to form a complex.

The Mitragotri reference, however, does not teach or suggest a method for delivery of proteins having at least a molecular weight of 150 kDa, much less a botulinum toxin. Instead, the Mitragotri reference only teaches transdermal delivery of proteins between the molecular weights of 6 kDa and 48 kDa. The Mitragotri reference at page 850.

The Smith reference relates to a method for treating a cellulite condition using a "cell renewal stimulant". Accordingly, the Smith reference teaches that a skin area can be stripped prior to applying a cell renewal stimulant (e.g., a retinoid, see claim 1). However, the Smith reference does not teach or suggest that an enzyme such as botulinum toxin may be applied to the stripped skin area, where the enzyme would penetrate to the subdermal layer of the skin. Further, from reading the specification of the Smith reference, one of ordinary skill would not be motivated to apply a botulinum toxin to the stripped area of skin, because a retinoid and a botulinum toxin are very different from each other and would be expected to have different skin penetration properties. For example, a retinoid (e.g., vitamin A) is a small molecule with a molecular weight of about 0.30 kDa., whereas the molecular weight of a botulinum toxin is about 150 kDa (900 kDa for the botulinum toxin complex). Since the penetration of molecules

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DOCKET NO.: ALLE0016-102 (17510 DIV2)

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through stripped skin partly depend on their sizes, one would have no basis to expect that botulinum toxin would penetrate through the stripped skin similarly to that of a retinoid, because botulinum toxin is much larger than the retinoid. Thus, the claimed invention is not obvious over the Smith reference alone, or in combination with the other secondary references.

The Ceve reference alone, or in combination with the other secondary references, fails to teach or suggest the step of non-chemically disrupting a skin area in conjunction with the application of a botulinum toxin, much less that such step will allow for the botulinum toxin to penetrate to the subdermal layer of the skin.

In view of the foregoing, Applicants submit that the pending claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Respectfully submitted,

Quan L. Nguyen

Registration No. 46,957

Date: October 31, 2005

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